Population Pharmacokinetics of Vancomycin in Intensive Care Patients with the Time-Varying Status of Temporary Mechanical Circulatory Support or Continuous Renal Replacement Therapy

Meng-Ta Tsai[a,b], Wei-Chun Wang[a], Jun-Neng Roan[b], Chwan-Yau Luo[c], Chen-Hsi Chou[a,d*]

[a] Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University Tainan City, Taiwan.

[b] Division of Cardiovascular Surgery, Department of Surgery, National Cheng Kung University Hospital and College of Medicine, Tainan City, Taiwan.

[c] Division of Cardiovascular Surgery, Department of Surgery, Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung City, Taiwan.

[d] School of Pharmacy, College of Medicine, National Cheng Kung University, Tainan City, Taiwan.

***Corresponding Author:**

Chen-Hsi Chou, PhD.

Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University No.1, University Road, Tainan City 701, Taiwan.

Tel.: +886 6 2353535 #5684

Fax: +886 6 2373149

Email: chenhsi@mail.ncku.edu.tw

https://orcid.org/0000-0003-0708-3657

Table S1 Tested model structures for clearance to conditionally include the effect of serum creatinine or dialysis

Model[a]	Formula for CL CL for non-dialysis / CL for dialysis	-2LL / Delta -2LL[b]	Model Parameter	RSE%		
				CL_dialysis		CL_cov_Cr
1	*tvCL x exp(nCL) x Cr* $^{CL\_cov\_Cr}$ *tvCL x exp(nCL) x exp(CL_dialysis)*	850.5 / 30.2	11	-128.1		-18.3
				tvCL_dialysis	tvCL_nondialysis	
2	*tvCL_non-dialysis x exp(nCL_non-dialysis) x Cr* $^{CL\_cov\_Cr}$ *tvCL_dialysis x exp(nCL_dialysis)*	848.0 / 32.7	12	14.7	8.0	-18.0
3	*tvCL_non-dialysis x exp(nCL) x Cr* $^{CL\_cov\_Cr}$ *tvCL_dialysis x exp(nCL)*	850.5 / 30.2	11	16.4	8.2	-18.1
4	*tvCL_non-dialysis x exp(nCL_nondialysis) x Cr* $^{CL\_cov\_Cr}$ *CL for non-dialysis + tvCL_dialysis x exp(nCL_dialysis)*	857.6 / 23.1	12	107.3	10.5	-34.5
5	*tvCL_non-dialysis x exp(nCL) x Cr* $^{CL\_cov\_Cr}$ *CL for non-dialysis + tvCL_dialysis x exp(nCL)*	858.0 / 22.7	11	107.5	10.6	-32.6

CL clearance, *RSE%* percent relative standard error of the estimate, *tvCL* typical or population value of clearance, *nCL* Eta or random effect or interindividual variability of clearance, *Cr* serum creatinine, *CL_cov_Cr* Cr as a covariate on CL

[a]Model 1: Dialysis and *Cr* as covariates on *CL*

Models 2 & 3: Independent typical value (tv) *tvCL* for non-dialysis or dialysis, with *Cr* as a covariate only on *CL* for non-dialysis.

Models 4 & 5 are based on models 2 & 3, but *CL* is the addition of *CL_non-dialysis on CL_dialysis* given any residual native renal function.

Model 3 was as the selected model structure for **CL**.

[b]Delta -2LL compared to the 2-compartment base model, P value all < 0.001

Table S2 Non-compartmental analysis results stratified by temporary mechanical circulatory support on the index dose

	tMCS	non-tMCS
	11	14
Dose amount (mg)	900.0 [750.0, 1000.0]	875.0 [637.5, 1187.5]
CL_obs (L/h)	1.6 [1.0, 3.5]	1.3 [1.0, 2.3]
Vd_obs (L)	35.6 [29.3, 48.4]	24.2 [21.4, 34.8]
Half-life (h)	12.6 [8.4, 44.7]	11.6 [10.8, 16.2]
C_max (mg/L)	26.5 [23.4, 29.6]	41.6 [28.9, 47.8]
C_last (mg/L)	13.6 [8.8, 16.5]	19.5 [11.8, 26.9]
CRRT	2 (18.2)	5 (35.7)
Body weight (kg)	67.8 [63.4, 80.9]	71.2 [60.4, 83.2]

tMCS temporary mechanical circulatory support, including ECMO or extracorporeal VAD, *Vd* volume of distribution, *CL* clearance, *CRRT* continuous renal replacement therapy, *C* Concentration

Table S3 Effects of covariates on reduction of -2LL or interindividual variability (IIV%)

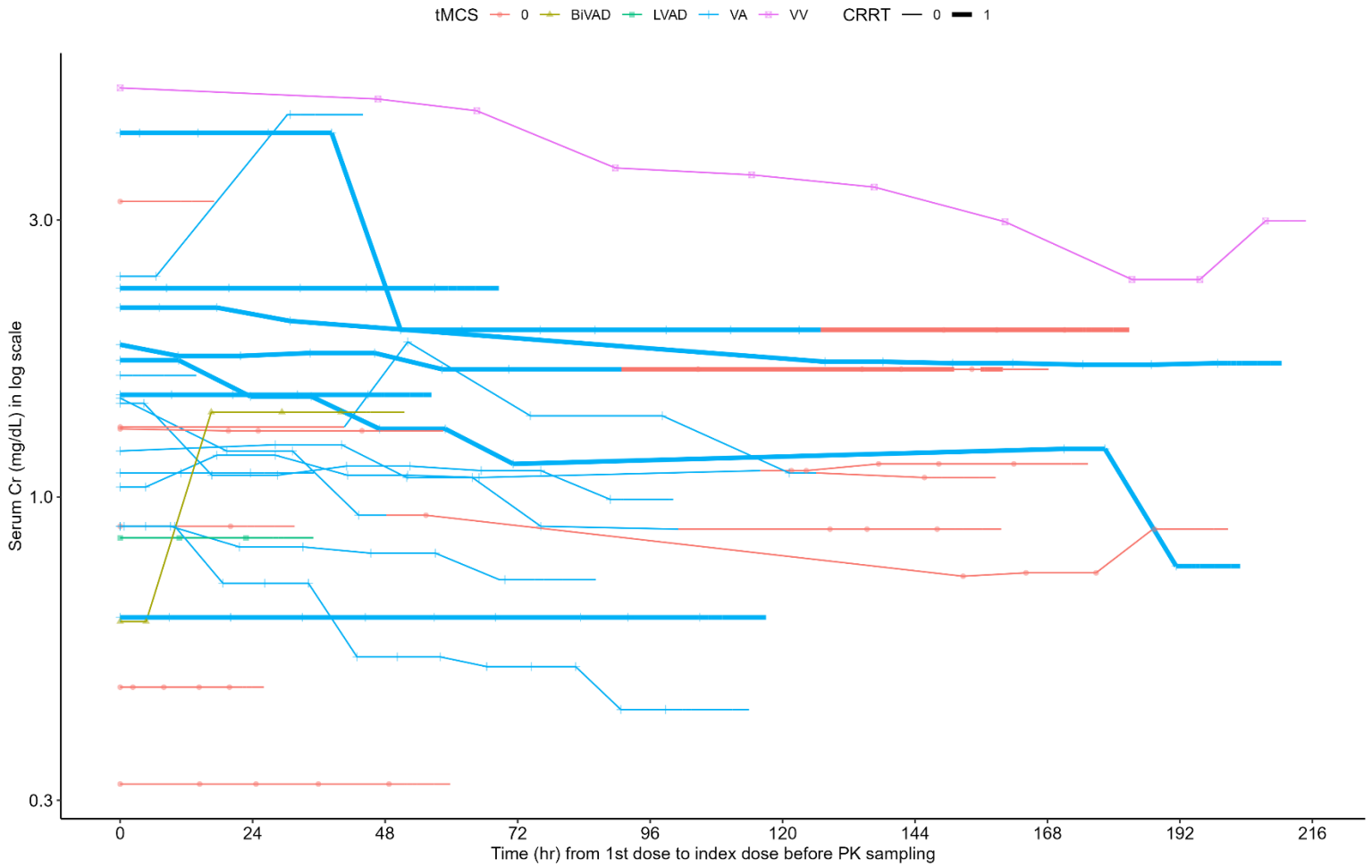
Model	-2LL	Delta -2LL	Parameter (n)	P value	IIV%			
					Vc	Vp	CL	Q
Two-compartment base model	880.7		9					
+ CL = CL_non-dialysis x Cr $^{CL\_non\text{-}dialysis\_Cr}$ or CL_dialysis if CRRT(+)	850.5	30.2	11	<0.001	0.10	36.4	36.9	50.3
+ tMCS on Q	839.6	10.9	12	<0.001	0.01	36.7	37.1	35.8
+ BW on CL	834.1	5.5	13	0.020	0.03	36.8	32.3	35.7
+ CRRT on Vc	817.9	16.2	14	<0.001	0.03	31.7	32.4	29.2

Vc volume of distribution of the central compartment, *Vp* volume of distribution of the peripheral compartment, *CL* clearance, *Q* intercompartment clearance, *Cr* serum creatinine, *CRRT* continuous renal replacement therapy, *tMCS* temporary mechanical circulatory support, *BW* body weight

Table S4 Model structure and estimates of published population PK study about vancomycin in ECMO

Author	Cpt	Vc (L/kg) (V1)	Vp (L/kg) (V2 / V3)	Vd (L/kg) (V1+V2+V3)	CL (L/h/kg)	Q (L/h/kg)	CL_dialysis (L/h/kg)	Covariate
Tsai et al this study	2	0.2 if non-CRRT 0.34 if CRRT	0.48	0.68 if non-CRRT 0.82 if CRRT	non-CRRT 0.041	0.269 if non-tMCS 0.140 if tMCS	CRRT 0.033	BW for CL, CRRT for Vc Cr for CL-nonCRRT tMCS for Q
Cheng et al 2022	2	0.39	NA	.	0.04	Kpc 2.11 (L/h) Kcp 0.94 (L/h)	0.0018	BW for Vc CrCL for CL
Jung, Lee & Kim 2021	3	0.108	0.208 V2 0.083 V3	0.40	0.054	0.067 Q2 0.123 Q3	.	CrCL for CL VA ECMO reduces Q
Moffett et al 2018	2	0.36	0.462	0.822	0.057	0.082	.	BW obligatory for all Age for Vc Albumin for Vp Cr, gestational age for CL
Moore et al 2016	2	0.25	0.34	0.59	0.0297	0.1179		BW for Vc, Vp Cr for CL
Wu et al 2016	1	0.83	.	0.83	0.0145	.	.	BW for Vc, CL Age for Vc
Donadello et al 2014	2	0.45	0.82	1.27	0.05	0.05	.	CRRT for CL
Mulla & Pooboni 2005	2	0.37 for age>4000days, 0.45 for age<4000days	0.25	0.62	0.04	0.09	.	BW obligatory for all Age for Vc and CL Cr for CL ECMO flow increases Q but not included in the model

Vc volume of distribution of the central compartment, *Vp* volume of distribution of the peripheral compartment, *Vd* volume of distribution, *BW* body weight, *CL* clearance, *Cr* serum creatinine, *CrCL* creatinine clearance, *Q* intercompartment clearance, *CRRT* continuous renal replacement therapy, *tMCS* temporary mechanical circulatory support, *ECMO* extracorporeal membrane oxygenation



Supplementary Fig. S1 Time-serial change of individual serum creatinine level (mg/dL, in log scale) and continuous renal replacement therapy (CRRT) or temporary mechanical circulatory support (tMCS) status of the twenty-five subjects in the modeling cohort from the first vancomycin dose to the index dose before PK sampling. BiVAD = biventricular assist device; LVAD = left ventricular assist device; VA = VA ECMO, VV = VV ECMO.